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Biomimetic Total Synthesis of Malbrancheamide and Malbrancheamide B

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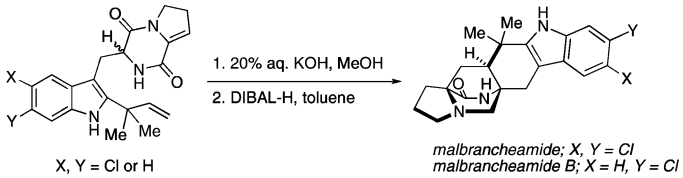
Received January 17, 2008



The biomimetic total syntheses of both malbrancheamide and malbrancheamide B are reported. The synthesis of the two monochloro species enabled the structure of malbrancheamide B to be unambiguously assigned. The syntheses each feature an intramolecular Diels−Alder reaction of a 5-hydroxypyrazin-2(1*H*)-one to construct the bicyclo[2.2.2]diazaoctane core, which has also been proposed as the biosynthetic route to these compounds.

Introduction

Our research group has exhibited a long-standing interest in the synthesis and biosynthetic study of a number of unique prenylated indole alkaloids containing a characteristic bicyclo-[2.2.2]diazaoctane core.[1] This class of natural products includes such highly biologically active fungal metabolites as the paraherquamides,[2] brevianamides,[3] notamides,[4] and stephacidins,[5] among others, which we have shown all arise biogenetically from tryptophan, mevalonate-derived isoprene units, and proline or derivatives of proline.[1] Sammes originally proposed that the bicyclo[2.2.2]diazaoctane core common to all of these natural products arises in *Nature* via an intramolecular hetero-Diels−Alder reaction of a 5-hydroxypyrazin-2(1*H*)-one,[6] and work from this laboratory has extensively supported such a proposal.[1] In fact, we have applied such a [4+2] hetero-Diels−Alder cycloaddition strategy to the total synthesis of several of these prenylated indole alkaloids, including stephacidin A,[7] brevianamide B,[8] marcfortine C,[9] notoamide B,[7b] and VM55599.[10]

Malbrancheamide (**1**)[11] and malbrancheamide B (**2**) were recently isolated from *Malbranchea aurantiaca* RRC1813, a

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10.1021/jo800116y CCC: $40.75
Published on Web 03/18/2008

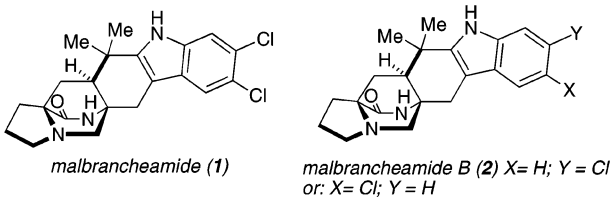


FIGURE 1. Malbrancheamide and malbrancheamide B.

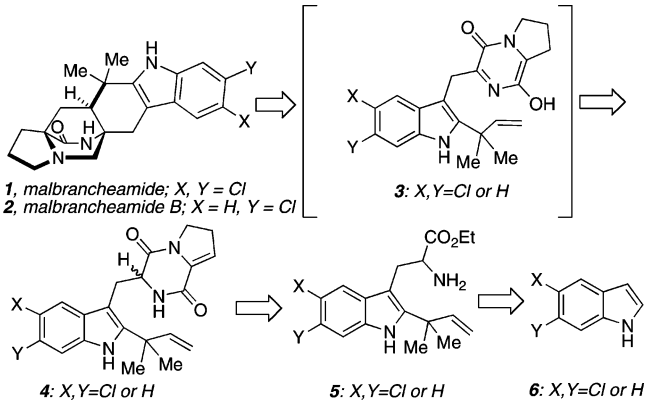
fungus collected on bat detritus collected in a cave in Mexico by Mata and co-workers. These new substances are the first alkaloids in this class of prenylated indole alkaloids to contain a halogenated indole ring (Figure 1). The lack of a tertiary amide in the bicyclo[2.2.2]diazaoctane core also serves to characterize the malbrancheamides. In addition to these notable structural features, malbrancheamide has been shown to be a calmodulin (CaM) antagonist that inhibits the activity of CaM-dependent phosphodiesterase (PDE1) in a concentration dependent manner.[11] The chemotherapeutic potential of PDE1 inhibitors includes applications in the treatment of neurodegenerative diseases, cancers, and vascular diseases, due to the effect on intracellular cAMP and cGMP concentrations.[12] New pharmacological properties of malbrancheamide may be discovered through the study of malbrancheamide, malbrancheamide B, and other analogs, as specific PDE1 inhibitors are scarce and the exact function of the enzyme has not been fully characterized.

Although compelling spectroscopic evidence indicated that the structure of **1** was as shown,[11] the precise structure of malbrancheamide B (**2**) was less certain. Isolation and structural characterization of **2** indicated the presence of a single chlorine on the indole ring, and further, preliminary biosynthetic experiments indicated that malbrancheamide B (**2**) is a putative biosynthetic precursor to **1**,[13] which is thought to arise by sequential halogenation events. However, the question as to whether malbrancheamide B (**2**) was constituted as the 5-chloro or the 6-chloro derivative was unclear from the preliminary characterization data due to the scarce supply of the natural material. With these issues at the forefront, we undertook the synthesis of both natural substances to determine the exact identity of malbrancheamide B. To this end, we envisioned that malbrancheamide (**1**) and malbrancheamide B (**2**) would arise from the aforementioned hetero-IMDA of the 5-hydroxypyrazin-2(1*H*)-one **3**, which we could access by enolization and tautomerization of the enamide **4** (Scheme 1). Using chemistry previously established in our laboratory,[7a] we planned on assembling the enamide **4** from a reverse prenylated tryptophan **5**, which could be obtained in a few steps from the corresponding chlorinated indole **6**.

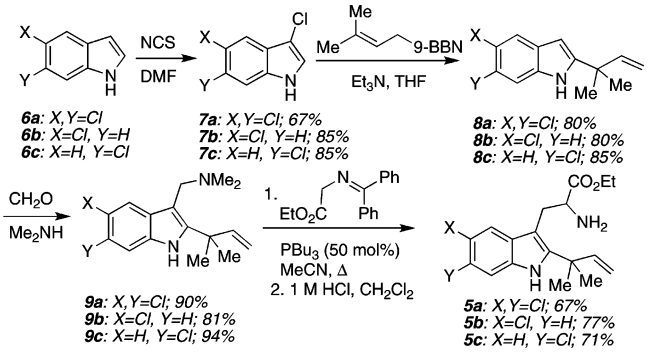
Results and Discussion

Installation of the reverse prenyl group at the indole 2-position was carried out using a two-step protocol developed by Danishefsky and co-workers.[14] Chlorination at the 3-position

SCHEME 1. Retrosynthetic Plan



SCHEME 2. Reverse Prenylated Tryptophan Derivatives



of indoles **6a**−**c**[15] using NCS in DMF gave **7a**−**c** (Scheme 2), which were treated with prenyl-9-BBN in the presence of Et_3N to afford the reverse prenylated indoles **8a**−**c**.[14] The corresponding gramines **9a**−**c** were prepared by treating **8a**−**c** with formaldehyde and dimethylamine, and subsequent Somei−Kametani coupling[16] and imine hydrolysis gave the tryptophan derivatives **5a**−**c** in good yields.

The free amine moieties in **5a**−**c** were protected as the corresponding BOC-carbamates followed by ester hydrolysis under standard conditions to yield acids **10a**−**c** (Scheme 3). Coupling of *cis*-3-hydroxyproline ethyl ester with the tryptophan derivatives **10a**−**c** in the presence of HATU delivered the amides **11a**−**c** as inseparable mixtures of diastereomers. Treatment of **11a**−**c** with TFA led to carbamate deprotection and the resulting amino esters were immediately cyclized to the corresponding diketopiperazines **12a**−**c** after refluxing with 2-hydroxypyridine. Dehydration of **12a**−**c** under Mitsunobu conditions gave the enamides **4a**−**c**, which would serve as the respective IMDA substrates.[17]

Treatment of the enamides **4a**−**c** with aqueous KOH in MeOH gave intermediate hydroxy-azadienes by enolization and tautomerizaion, and subsequent IMDA gave mixtures of **13a**−**c** and **14a**−**c** favoring the desired *syn*-isomers **13a**−**c** in ratios of (2−1.6):1 (Scheme 4). The observed preference for the IMDA to provide the *syn*-isomers **13a**−**c** as the major products mirrors

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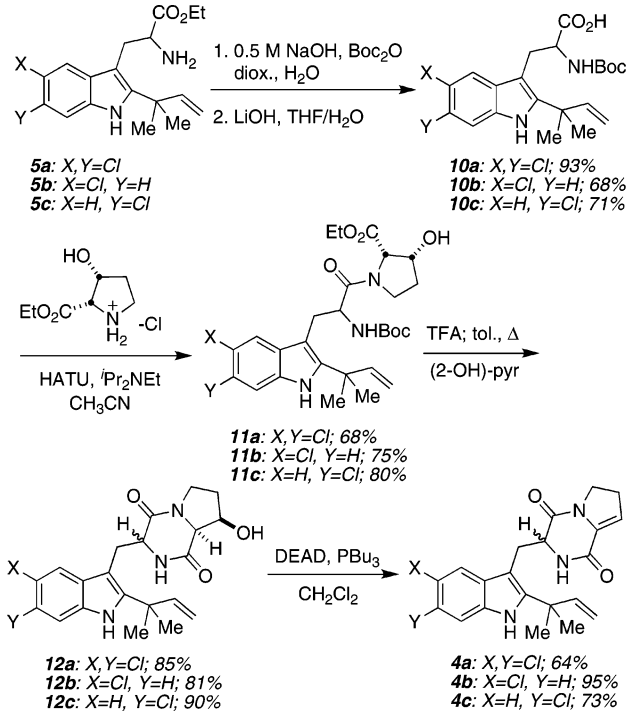
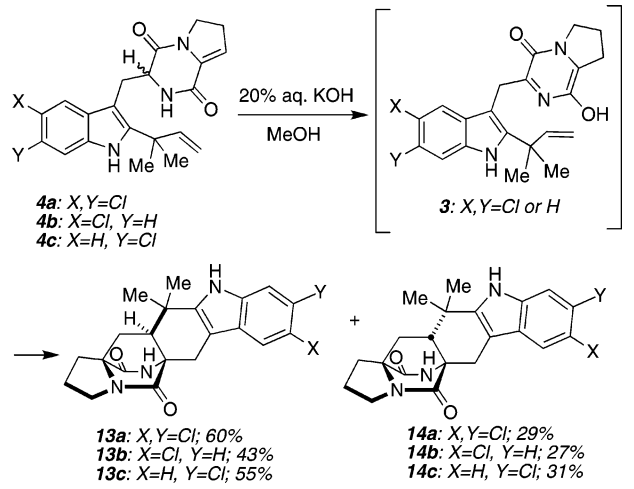
(17) Curiously, attempts to effect the one-step dehydration/IMDA reaction sequence from **12a**−**c** directly to **13a**−**c** + **14a**−**c** failed under the same conditions used successfully for stephacidin A (ref 7a) and marcfortine C (ref 9).

SCHEME 3. Enamide Diels−Alder Precursors



SCHEME 4. Hetero-IMDA Reactions



the preference we have noted for this cycloaddition in the past.[7−9] Considering that previous optimization efforts to improve the *syn*:*anti* ratio in related IMDAs were not productive when a variety of solvents and temperatures were studied, we elected to simply separate the major isomers **13a−c** and continue the total syntheses without further optimization.[7−9]

Completion of the syntheses required selective reduction of the tertiary amide in the presence of the secondary amide, and to that end, **13a−c** were treated with excess DIBAL-H,[18] which cleanly provided malbrancheamide (**1**) from **12a** (80%) and malbrancheamide B (**2**) from **12c** (74%) (Scheme 5). Synthetic **1** was identical in all respects (^{1}H, ^{13}C, HRMS) to the natural product.[11] Comparison of the ^{1}H NMR spectrum of **15**, the 5-chloro derivative, to that of natural malbrancheamide B revealed significant differences in the aromatic region revealing that the correct structure contained a 6-chloroindole ring.

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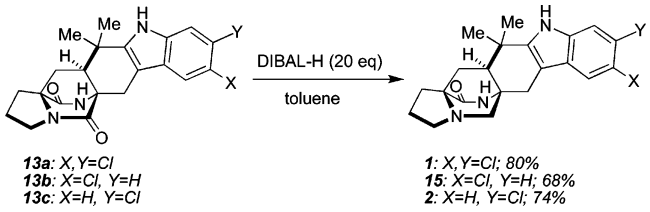
SCHEME 5. Amide Reductions



Gratifyingly, synthetic **2** was identical in all respects (^{1}H, HRMS) to natural malbrancheamide B.

It is striking that the initial halogenation of the indole ring during the biosynthesis of malbrancheamide B, occurs at the less-activated 6-position as opposed to the more electron-rich 5-position. Studies to clone and express the putative halogenase from *M. aurantiaca* are currently under investigation in these laboratories.

In summary, the first total synthesis of malbrancheamide (**1**) and malbrancheamide B (**2**) have been completed in twelve steps in 5.3% and 8.2% overall yield, respectively. In addition, the structure of malbrancheamide B (**2**) was confirmed though the synthesis of both the 5-chloro and the 6-chloro regioisomers. Experiments to establish the biosynthetic relationship between **1** and **2** and their putative progenitors are in progress and will be reported in due course.

Experimental Section

Representative Procedure for the Hetero-Diels−Alder Reaction of Enamides 4. Preparation of Cycloadducts 13a and 14a. To a solution of **4a** (86 mg, 0.21 mmol) in MeOH (16 mL) at 0 °C was added 20% aqueous KOH (4 mL). The reaction was warmed to room temperature (rt) and was stirred for 12 h. The reaction was quenched with sat. NH_4Cl (30 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was triturated with $CHCl_3$ (30 mL), and the suspension was filtered to provide 53 mg (60%) of **13a** as a white amorphous solid. Concentration of the filtrate gave 25 mg (29%) of **14a** as a white amorphous solid. Data for major isomer **13a**: ^{1}H NMR (300 MHz, CD_3OD) δ 7.55 (s, 1 H), 7.40 (s, 1 H), 3.57 (d, J = 15.5 Hz, 1 H), 3.47 (m, 1 H), 2.74 (d, J = 15.5 Hz, 1 H), 2.60 (m, 1 H), 2.20−1.96 (comp, 6 H), 1.35 (s, 3 H), 1.11 (s, 3 H); ^{13}C NMR (75 MHz, CD_3OD) δ 175.7, 171.3, 144.3, 137.2, 128.1, 125.4, 123.3, 119.8, 113.1, 104.8, 68.3, 61.6, 50.8, 45.2, 36.2, 31.7, 30.1, 28.6, 25.4, 24.9, 22.3; IR (neat) 1663, 1428 cm^{-1}; HRMS (TOF+) calcd for $C_{21}H_{22}N_3O_2Cl_2$ (M + H) 418.1084, found 418.1084. Data for minor isomer **14a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.78 (s, 1 H), 7.49 (s, 1 H), 7.33 (s, 1 H), 3.71 (d, J = 17.8 Hz, 1 H), 3.47 (comp, 2 H), 3.25 (s, 1 H), 2.78 (d, J = 17.8 Hz, 1 H), 2.67 (m, 1 H), 2.18−1.78 (comp, 6 H), 1.24 (s, 3H), 1.16 (s, 3 H); ^{13}C NMR (75 MHz, CD_3OD /$CDCl_3$ (1:9)) δ 173.7, 169.6, 142.6, 135.7, 127.1, 125.0, 122.9, 119.1, 112.4, 102.9 67.2, 61.5, 45.8, 44.3, 34.8, 32.6, 29.8, 29.1, 28.4, 24.5, 23.2; IR (neat) 1676, 1453 cm^{-1}; HRMS (TOF+) calcd for $C_{21}H_{22}N_3O_2Cl_2$ (M + H) 418.1084, found 418.1079.

Cycloadducts 13b and 14b. Prepared from **4b** in to give 43% of **13b** as a white amorphous solid and 27% of **14b** as a white amorphous solid according to the representative procedure described above for **13a** and **14a**. Data for major isomer **13b**: ^{1}H NMR (300 MHz, CD_3OD) δ 7.54 (s, 1 H), 7.44 (s, 1 H), 7.22 (d, J = 8.6 Hz, 1 H), 7.04 (d, J = 8.6 Hz, 1 H), 3.68 (d, J = 15.4 Hz, 1 H), 3.55−3.40 (comp, 2 H), 2.77 (d, J = 15.4 Hz, 1 H), 2.76 (m, 1 H), 2.61 (m, 1 H), 2.25−1.92 (comp, 5 H), 1.37 (s, 3 H), 1.12 (s, 3 H); ^{13}C NMR (100 MHz, CD_3OD) δ 175.8, 171.4, 143.4, 136.8, 129.2, 125.2, 122.1, 118.2, 112.8, 104.5, 68.3, 61.6, 50.8, 45.2, 36.2, 31.7, 30.1, 28.7, 25.5, 25.0, 22.4; IR (neat) 1678, 1441 cm^{-1}; HRMS

(TOF+) calcd for $C_{21}H_{23}N_3O_2Cl$ (M + H) 384.1473, found 384.1460. Data for minor isomer **14b**: ^{1}H NMR (300 MHz, CD_3OD) δ 7.91 (s, 1 H), 7.41 (d, J = 2.0 Hz, 1 H), 7.23 (d, J = 8.6 Hz, 1 H), 7.01 (dd, J = 8.6, 2.0 Hz, 1H), 3.71 (d, J = 17.6 Hz, 1H), 3.53 (comp, 2 H), 2.90 (d, J = 17.6 Hz, 1 H), 2.70 (m, 1 H), 2.23−1.89 (comp, 6 H), 1.34 (s, 3 H), 1.27 (s, 3 H); ^{13}C NMR (100 MHz, CD_3OD) δ 175.4, 171.7, 143.4, 136.8, 129.7, 125.3, 122.1, 118.1, 112.8, 103.8, 68.6, 62.7, 47.3, 45.2, 35.9, 33.3, 30.8, 29.9, 28.7, 25.4, 24.8, 23.8; IR (neat) 1675, 1461 cm^{-1}; HRMS (TOF+) calcd for $C_{21}H_{23}N_3O_2Cl$ (M + H) 384.1473, found 384.1468.

Cycloadducts 13c and 14c. Prepared from **4c** in to give 55% of **13c** as a white amorphous solid and 31% of **14c** as a white amorphous solid according to the representative procedure described above for **13a** and **14a**; data for major isomer **13c**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.75 (s, 1 H), 7.40−6.98 (comp, 3 H), 3.42 (d, J = 15.3 Hz, 1 H), 3.30 (comp, 2 H), 2.68 (d, J = 15.3 Hz, 1 H), 2.50 (comp, 1 H), 2.10−1.70 (comp, 6 H), 1.27 (s, 3 H), 0.99 (s, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.0, 168.4, 142.0, 136.8, 125.3, 125.2, 118.9, 118.5, 110.4, 103.8, 66.0, 59.6, 48.9, 43.6, 34.6, 30.0, 28.7, 27.9, 24.0, 23.7, 21.6; IR (neat) 1671, 1409 cm^{-1}; HRMS (TOF+) calcd for $C_{21}H_{23}N_3O_2Cl$ (M+H) 384.1473, found 384.1470. Data for minor isomer **14c**: ^{1}H NMR (400 MHz, $CD_3OD/CDCl_3$ (1:9)) δ 9.58 (s, 1 H), 7.33 (d, J = 8.4 Hz, 1 H), 7.23 (d, J = 1.8 Hz, 1 H), 6.97 (dd, J = 8.4, 1.8 Hz, 1 H), 3.75 (d, J = 17.8 Hz, 1 H), 3.47 (comp, 2 H), 3.30 (bs, 1 H), 2.84 (d, J = 17.8 Hz, 1 H), 2.70 (m, 1 H), 2.23−1.77 (comp, 6 H), 1.25 (s, 3 H), 1.18 (s, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.43, 169.0, 142.0, 136.8, 125.8, 125.3, 119.0, 118.5, 110.4, 103.1, 79.2, 66.4, 60.5, 45.4, 43.7, 34.2, 31.6, 28.6, 27.7, 24.0, 22.5; IR (neat) 1672, 1410 cm^{-1}; HRMS (TOF+) calcd for $C_{21}H_{23}N_3O_2Cl$ (M + H) 384.1473, found 384.1468.

Representative Procedure for the Selective Reduction of Tertiary Amides with Excess DIBAL-H. Synthesis of Malbrancheamide (1). DIBAL-H (0.70 mL, 1 M in toluene, 0.70 mmol) was added to a suspension of **13a** (15 mg, 0.036 mmol) in toluene (7 mL) at rt. The reaction was stirred at rt for 12 h, whereupon finely powdered $Na_2SO_4 \cdot 10H_2O$ was added until bubbling ceased. The mixture was filtered with a medium porosity fritted funnel washing with EtOAc (50 mL) and MeOH (50 mL), and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography eluting with MeOH/CH_2Cl_2 (2:98) to give 12 mg (80%) of **1** as a white amorphous solid: ^{1}H NMR (400 MHz, CD_3OD) δ 7.48 (s, 1 H), 7.40 (s, 1 H), 3.43 (d, J = 10.3 Hz, 1 H), 3.06 (m, 1 H), 2.85 (comp, 2 H), 2.54 (m, 1 H), 2.27 (dd, J = 10.2, 1.5 Hz, 1 H), 2.20−1.18 (comp, 6 H), 1.43 (s, 3 H), 1.34 (s, 3 H); ^{13}C NMR (100 MHz, CD_3OD) δ 176.6, 145.1, 137.3, 128.2, 125.3, 123.2, 119.6, 113.1, 104.7, 66.1, 59.4, 57.4, 55.4, 48.5, 35.5, 32.4, 30.6, 30.0, 28.1, 24.2, 23.5; IR (neat) 3226, 1658, 1460 cm^{-1}; HRMS (TOF+) calcd for $C_{21}H_{24}N_3OCl_2$ (M + H) 404.1291, found 404.1290.

Isomalbrancheamide B (15). Prepared from **13b** in 68% yield as a white amorphous solid according to the representative procedure described above for **1**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 (s, 1 H), 7.33 (s, 1 H), 7.26 (d, J = 8.5 Hz, 1 H), 7.01 (d, J = 8.5 Hz, 1 H), 3.33 (d, J = 7.2 Hz, 1 H), 3.26 (d, J = 9.9 Hz, 1 H), 2.76 (s, 2 H), 2.42 (m, 1 H), 2.15−1.73 (comp, 7 H), 1.33 (s, 3 H), 1.27 (s, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.1. 143.4, 134.9, 127.7, 122.8, 120.4, 116.7, 112.1, 103.4, 64.1, 58.6, 55.3, 53.9, 47.0, 34.0, 31.1, 30.0, 28.7, 26.6, 23.7, 22.5; IR (neat) 3311, 1637, 1458 cm^{-1}; HRMS (TOF+) calcd for $C_{21}H_{25}N_3OCl$ (M + H) 370.1680, found 370.1675.

Malbrancheamide B (2). Prepared from **13c** in 74% yield as a white amorphous solid according to the representative procedure described above for **1**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.41 (s, 1 H), 7.32 (d, J = 8.4 Hz, 1 H), 7.27 (d, J = 1.7 Hz, 1 H), 6.95 (dd, J = 8.4, 1.7 Hz, 1 H), 3.36 (s, 1 H), 3.27 (d, J = 10.0 Hz, 1 H), 2.95 (m, 1 H), 2.76 (s, 2 H), 2.43 (m, 1 H), 2.13 (d, J = 9.9 Hz, 1 H), 2.10−1.70 (comp, 6 H), 1.32 (s, 3 H), 1.26 (s, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.1, 142.6, 136.8, 125.3, 125.2, 118.7, 118.5, 110.3, 103.7, 64.1, 58.5, 55.3, 53.9, 47.0, 34.0, 31.1, 30.0, 28.7, 26.6, 23.7, 22.5; IR (neat) 3297, 1652, 1457 cm^{-1}; HRMS (TOF+) calcd for $C_{21}H_{25}N_3OCl$ (M + H) 370.1680, found 370.1670.

Acknowledgment. Financial support from the National Institutes of Health (CA70375 to R.M.W) and the Hans W. Vahlteich Professorship (to D.H.S.) is gratefully acknowledged. We are grateful to Prof. Rachel Mata and Dr. María del Carmen González of the Departamento de Farmacia, Facultad de Química, Universidad Nacional Autónoma de México for providing ^{1}H NMR spectra of natural malbrancheamide and malbrancheamide B as well as an authentic specimen of malbrancheamide. We also acknowledge Prof. Mata for sharing a pre-print of their manuscript describing the structural elucidation of malbrancheamide B (ref 11b). We thank Dr. Anthony E. Glenn of the USDA for providing M. aurantiaca RRC1813 strain (originally obtained from Dr. María del Carmen González). Mass spectra were obtained on instruments supported by the NIH Shared Instrumentation Grant GM49631.

Supporting Information Available: Spectroscopic data and experimental details for the preparation of all new compounds as well as copies of ^{1}H NMR and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

JO800116Y